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Quorumpeps database: chemical space, microbial origin and functionality of quorum sensing peptides

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ABSTRACT

Quorum-sensing (QS) peptides are biologically attractive molecules, with a wide diversity of structures and prone to modifications altering or presenting new functionalities. Therefore, the Quorumpeps database (http://quorumpeps.ugent.be) is developed to give a structured overview of the QS oligopeptides, describing their microbial origin (species), functionality (method, result and receptor), peptide links and chemical characteristics (3D-structure-derived physicochemical properties). The chemical diversity observed within this group of QS signalling molecules can be used to develop new synthetic bio-active compounds.

INTRODUCTION

Quorum sensing (QS) enables bacterial cells to establish cell–cell communication and to regulate the expression of specific genes in response to local changes in cell density (1,2). The concept of intercellular communication within bacterial populations originates from two independent discoveries in the 1960s and 1970s. In 1965, Tomasz (3) stated that a hormone-like extracellular peptide was important for genetic competence in *Streptococcus pneumoniae*. In 1970, Hastings and co-workers reported that luminescence in the marine bacterium *Vibrio fischeri* was produced only at high cell density, but not in dilute suspensions. They called the responsible component 'autoinducer', which was later identified as *N*-(3-oxohexanoyl)-homoserine lactone (4,5).

Several classes of microbially derived signalling molecules have now been identified. In general, Gram-negative QS bacteria use acylated homoserine lactones (AHLs) as autoinducers, while Gram-positive bacteria predominantly communicate with each other using oligopeptides that often contain chemical modifications (6). In addition, a third family of compounds termed as autoinducer-2, derived from the common precursor 4,5-dihydroxy-2,3-pentanedione, has been found to be widespread in the bacterial world (7). Using these QS signalling molecules, bacteria are able to regulate a diverse array of physiological activities in a cell-density-dependent manner. Processes controlled by QS are usually those that are unproductive when undertaken by an individual bacterium, but become effective when undertaken by a group. Thus, QS allows bacteria to behave like a multicellular organism. In addition to genetic competence, bioluminescence, conjugation and swarming motility, QS also controls virulence factor secretion, biofilm formation and sporulation (6,8–10).

In the past decade, a significant increase in interest in bacterial QS is noticed. The discovery of the QS-mediated virulence factor expression in many clinically relevant pathogens raised the idea of QS antagonist production. Blocking QS is now recognized as a viable approach for the development of novel antibiotics (11). Moreover, the increased antimicrobial resistance, due to e.g. the formation of a biofilm in which the micro-organisms are protected against antimicrobial chemotherapy and the immune system of the host, has called the attention to the QS system (12). Intriguingly, recent evidence indicates chemical communication not only between bacteria of different species but also between bacteria and host as well. For example, AHLs have been found to be directly recognized by eukaryotic cells and even to influence the behaviour of eukaryotic organisms (immune suppression and blood vessel relaxation) (2,13). These QS signalling peptides may thus have diagnostic and therapeutic properties in oncology and other pathologies as well (14).

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Peptides have recently attracted renewed attention for their use in research, disease prevention, diagnosis and/or therapy. These physiologically active molecules demonstrate high affinity, strong selectivity and low toxicity and can be synthetically modified in order to optimize their affinity for a particular receptor and to display a more specific biodistribution pattern (15,16). The main drawback of the use of peptide-based compounds is their low stability to peptidases and proteases found in most tissues (16). However, metabolic stability can be increased by substitution of unnatural amino acids or D-isomers, amidation or acetylation of peptide termini, cyclization and so on, hereby increasing the probability of obtaining useful drugs, structurally related to the parent lead peptides (17,18). Peptides can thus reverse the increased attrition rate observed with small-molecule drugs.

Seen the increased interest in bacterial QS signalling molecules and the potential of peptides as new therapeutic or diagnostic drugs, we present here a database of (modified) QS peptides with the acronym 'Quorumpeps' (http://quorumpeps.ugent.be). This database encompasses the structures and microbial origin as well as functionality responses of the QS-derived signalling peptides, as described in the literature.

ORGANIZATION OF THE DATABASE

Data model

In order to list all relevant data about the QS signalling peptides, a relational database is constructed (19). The usage of such a relational model facilitates the insertion of new and/or additional data. Moreover, it avoids the occurrence of duplicate data and data inconsistencies to the largest extent possible. The schematic database model is available through the Quorumpeps website (Supplementary Figure S1). In this visual representation, each block describes the structure of a table, with the table name mentioned in the header of the block. In each block, the names of the columns are listed. The column names marked in bold font together determine the primary key of the table. This means that the combination of values for these columns is unique for each row in the table. For clarity, the primary key columns are separated from the other columns by means of a dotted line. Relationships between tables are symbolized by an arrow.

The central table in the Quorumpeps database model is 'Experiment', representing the binding analysis of a peptide (identified by MoleculeID) with a specific receptor (identified by ReceptorName), using a given method (identified by MethodName). The resulting response (result type, measurement and unit) is also given in this table. The table 'Molecule' summarizes the chemical information about the peptides, including the peptide name, the peptide chemical sequence, the simplified molecular input line entry specification (SMILES) string and some physicochemical properties. Moreover, also the optimized 3D-structure is given in the database in .HIN format, acquired using HyperChem 8.0 (Hypercube, Gainesville, FL, USA). The bacterium that produces the signalling molecule is given in the table 'Origin', while derived molecules are connected to the molecules from which they are derived through the table 'Molecule_Modification'. The receptors are listed in the table 'Receptor'. All methods used to analyse the functionality of the peptides and the references used are summarized in the tables 'Method' and 'Publication', respectively. The observed activity (e.g. agonist or antagonist) of a peptide, bound to a specific receptor, is stored in the additional table 'Binding'.

The Quorumpeps database has been implemented on a MySQL backend and is publicly available through the website http://quorumpeps.ugent.be. The website is implemented by using the content management system Drupal and provides a simple, keyword-based search interface to access the data available. Several search options are presented: peptide information (including sequence, trivial name, SMILES or molecular formula), origin, functionality method, receptor and literature information. Each performed search results in an overview of peptides that match the query. From this overview page, detailed information about the selected peptides or related literature can be obtained. User information can be found at the help page of the Quorumpeps website.

Data collection

For loading information in the database, literature data were gathered by using the search engines Web of Knowledge, PubMed and Google, covering the period 1955–2012. The terms 'QS', 'autoinducer' and 'pheromone', each separately, as well as 'peptide', 'agonist' and 'antagonist', using the Boolean operation 'AND', were used. The obtained literature was processed manually and all relevant information was put in the database. In order to expand the data available in the database, a data submission page has been constructed on the website allowing researchers to inform us of new information.

QUORUMPEPS IN DETAIL

Chemical information

The chemical information about the QS peptides includes the IUPAC one-letter code amino acid sequence, with or without any (post-translational) modification, trivial name, SMILES, molecular formula and physicochemical properties (molecular weight, logP and isoelectric point (pI)). The trivial name comprises every name that is given to the specific peptide, thus allowing group names (e.g. autoinducing peptide) as well as individual peptide names (e.g. PhrA).

Before calculating the different physicochemical properties, the geometrical structure of these QS peptides was optimized using HyperChem 8.0. The geometry optimization was obtained by the molecular mechanics force field method using the Polak–Ribière conjugate gradient algorithm with a root mean square gradient of $0.1\,\text{kcal}/(\text{Å} \times \text{mol})$ as stop criterion. Afterwards, these Cartesian coordinate matrices were used to calculate the different descriptors, using HyperChem 8.0 and Marvin Beans 5.3.3 (Chemaxon,

Budapest, Hungary) software programs. This optimized .HIN structure is available through the Quorumpeps website, together with the 2D-SMILES notation. These formats allow the user to perform any sort of analysis on their various chemical properties, e.g. quantitative structure-activity relationship (QSAR) or multivariate data analysis (20). Diversity analysis using the diversity index (described by the Tanimoto coefficient) of the 231 QS peptides currently available in the Quorumpeps database indicated that this dataset is extremely diverse (DI = 0.21) and thus suitable for QSAR or quantitative structure–property relationship (QSPR) studies (21,22).

Species origin

In general, QS peptides are synthesized by Gram-positive bacteria, e.g. *Staphylococcus aureus* and *Bacillus subtilis*. As numerous different species are reported in the literature, an overview of all listed bacteria is available at the Quorumpeps homepage, by using the information-icon: using this scroll-list, rapid-directed searches can be performed by the user of Quorumpeps.

Chemical modifications (e.g. amino acid substitution) of an original QS peptide are visualized in the 'Species origin' section by referring to its original counterpart.

Functionality

The functional properties of the QS signalling peptides are described in the Quorumpeps database. Moreover, an overview of the receptors and methods can be found at the homepage of Quorumpeps, using the information-icon next to the appropriate characteristic.

The functionality of the signalling peptides is characterized by the method used to study their QS activity. The methods are using either the isolated signalling peptides or the (genetically modified) bacteria to investigate a biological activity. The target genes or their products are then qualitatively or quantitatively measured using antibacterial assays (23,24), biosensors (25–31), biofilm assays (32,33), analytical and immunoassays (34,35), DNA and RNA detection (36,37) or viability measurements (34,38–41). Moreover, different QS pathways are reported, which can be divided into mainly cell membrane receptor-mediated activation and, to a much lesser amount, cytoplasmic receptor activation after cell penetration of the peptides. The majority of QS peptides initiates a signalling pathway by activating a membrane-integrated histidine kinase, after which the cytoplasmic response regulator mediates the output response. This cascade of reactions is species specific, with homology seen between the different organisms. Different pathways can be distinguished, which are given in the Quorumpeps database: AgrC/AgrA and TRAP virulence system (42–47), ComD/ComE competence system (48), ComP/ComA and Rap competence or sporulation system (49–52), FsrC/FsrA virulence system (53) and NisK/NisR system or analogues (54,55). Furthermore, also the quantitative binding results of the QS peptides with a specific receptor are given in the Quorumpeps database, in which agonistic or antagonistic properties can be distinguished.

Links

This 'Links' section allows the user of Quorumpeps to link the reported QS peptides through their binding properties (i.e. receptor) or microbial origin. Peptides that bind with the same receptor as the selected peptide are given in the appropriate table, differentiating them based on their agonist or antagonist activity. Moreover, peptides that are synthesized by the same species are again listed in this information section.

Literature

All information gathered to develop this Quorumpeps database is summarized in the 'Literature' section, described by a publication-ID; detailed information is obtained after ID-selection: journal name, title, year and author names in the same order as they appear on the publication. Moreover, the possibility to download this publication is also available, through their PubMed ID number and related link.

CONCLUSION

This database (http://quorumpeps.ugent.be) gives an overview of reported QS signalling peptides and their derivatives, summarizing their chemical and functional properties, together with species information. Therefore, this database can function as a useful tool to justify peptide choices for evaluating different responses or to study QSPRs of these QS molecules. Quorumpeps will quarterly be updated by the authors, ensuring up-to-date information of this interesting and expanding field for other researchers.

SUPPLEMENTARY DATA

Supplementary Data are available at NAR Online: Supplementary Figure 1.

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